PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SUBRAMANAM, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi 110 048
INDE

PCT 20 DEC 2004

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	04.11.2004
Applicant's or agent's file reference SN&A SUVN-RK-005	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 03/00224	19.06.2003	21.06.2002

Applicant
SUVEN LIFE SCIENCES LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hebert, W Tel. +49 89 2399-2152

PATENT COOPERATION TREATY

PCT

RD 05 NOV 2004
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

20 DEC 2004

Applicant's or agent's file reference SUVN-RK-005	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 03/00224	International filing date *(day/month/year)* 19.06.2003	Priority date *(day/month/year)* 21.06.2002
International Patent Classification (IPC) or both national classification and IPC C07D487/04		
Applicant SUVEN LIFE SCIENCES LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 42 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.01.2004	04.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Goss, I Telephone No. +49 89 2399-8292

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00224

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

7, 15-18	as originally filed
19	received on 17.05.2004 with letter of 11.05.2004
1-6, 6a, 8-12, 12a, 12b, 13, 14, 20-37	received on 20.09.2004 with letter of 16.09.2004

Claims, Numbers

1-19	received on 20.09.2004 with letter of 16.09.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15-18

   because:

   ☒ the said international application, or the said claims Nos. 15-18 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-19
	No: Claims	
Inventive step (IS)	Yes: Claims	1-19
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-19
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15 to 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The present application relates to compounds characterized by the tetracyclic arylalkyl indoles structure core wherein the many substituents R_0, R_1 to R_{12} may be the same or different and each independently represent hydrogen or other specific group. The tetracyclic arylalkyl structure substituted at position 11 was already well known from many documents cited in the search report.

The applicant reconsidered the novelty objection based on the many novelty destroying disclosures and redefined the subject-matter claimed in term of positive features (without use of proviso or disclaimer but only restricting the whole scope).
The amended set of claims is allowable since the shrinking of the generic formula due to the limitation of the substituents R_1 to R_{12} together with the limitation of the definition of the group R_{13} and R_{14} did not lead to a particular combination of specific meanings of the respective residues which was not disclosed originally.

Inventive step

The problem underlying the present application appears to reside in the provision of further tetracyclic arylalkyl indoles and i.a. their derivatives and pharmaceutically acceptable compositions containing them.
The compounds of the general formula (I) of the present application are described as 5-HT (serotonin) ligands and/or melatonin receptor modulators .

The prior art cited in the search report also deal with melatonin analogues as hypnotics and as agents for restoring circadian rhythms (D1) as well as compounds useful in "treating neurological and psychiatric disorders such as ..." page 39 of D5 as also listed

on page 1 of the description.

In view of the fact that many novelty destroying compounds were known from the cited prior art and have almost the same pharmacological profile, the subject-matter claimed has been drastically restricted (as already pointed out above in the novelty analysis). Data are given in order to substantiate the inventive step of the claimed compounds, and the Applicant was reminded that the problem to be solved must be of a **technical** nature whereas the one apparently solved by the present application relates only to the mechanism of action of the relevant compounds (namely in terms of affinities of the compounds of the invention for the various serotonin receptors).

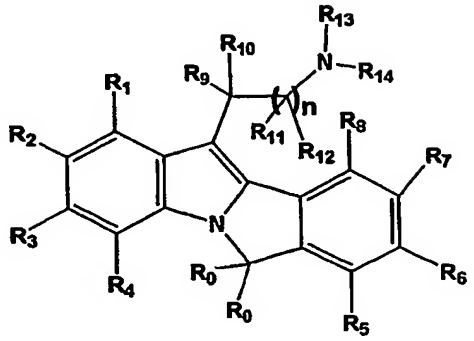
The EPO would request further evidences in order to show that the compounds claimed are indeed suitable in the treatment of i.a. emesis, nausea, gastric symptoms or mild cognitive impairment **(as also many of the compounds from the prior art are)** as functional evidences in addition to the binding characteristics of the compounds claimed. Also terms such as "aryl, heterocyclic or heteroaralkyl" used in claim 1, are considered to be non-limitative and embraces an infinite number of possibilities not yet explored by the Applicant. This will also be treated eventually during the European phase.

Industrial applicability

For the assessment of the present claims 15 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims:

1. A compound of the general formula (I),



General Formula (I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts and solvates,

wherein R_0 is either hydrogen or linear or branched $(C_1\text{-}C_2)$alkyl;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkylthio, aminocarbonylamino, dialkylaminocarbonylamino, carboxylic acid and its derivatives,

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_4)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

"n" is an integer ranging from 1 to 6.8, preferably 1 to 4. The carbon chains which 'n' represents may be either linear or branched.

2. A compound according to Claim -1, which is selected from the group consisting of:
11-(2-N,N-Dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole hydrochloride salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole maleic acid salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole D,L-malic acid salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole oxalate salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt;
2-Fluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt;
2-Fluoro-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N-cyclopropyl-N-methylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt;
2-Fluoro-11-(2-N-cyclopropyl-N-methylaminoethyl)-6*H*-isoindolo[2,1-a]indole;

11-(2-N,N-Dimethylaminoethyl)-2-methyl-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylaminoethyl)-2-methoxy-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-N-methyl-N-cyclopropylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
4-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
3,4-Dichloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
1-Chloro-11-(2-N,N-dimethylaminoethyl)-4-methyl-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-(2-N,N-dimethylaminoethyl)-4-methyl-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-[(2-N-methylamino)ethyl]-4-methyl-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-[(2-N-methyl-N-acetylamino)ethyl]-4-methyl-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-[(2-N-methylamino)ethyl]-2-methoxy-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-[(2-N-methylamino)ethyl]-2-sulfoamido-6*H*-isoindolo[2,1-a]indole;
3-Iodo-11-[(2-N-methylamino)ethyl]-2-methoxy-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylaminoethyl)-4-trifluoromethyl-6*H*-isoindolo[2,1-a]indole;
2,4-Difluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
11-(2-Pyrrolidin-1-ylethyl)-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-pyrrolidin-1-ylethyl)-6*H*-isoindolo[2,1-a]indole;
11-(2-(Piperidin-1-yl)ethyl)-6*H*-isoindolo[2,1-a]indole;
11-(2-(4-Methylpiperazin-1-yl)ethyl)-6*H*-isoindolo[2,1-a]indole;
11-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylaminoethyl)-4-ethyl-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylamino-1-hydroxyethyl)-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylaminoethyl)-4-methoxy-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
4-Bromo-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
4-Fluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-(4-methylpiperazin-1-yl)ethyl)-6*H*-isoindolo[2,1-a]indole; and
its stereoisomers, its N-oxides, its polymorphs, its pharmaceutically acceptable salts and solvates.

3. A pharmaceutical composition comprising either of a pharmaceutically acceptable carrier, diluent/s, excipient/s or solvates along with a therapeutically effective amount of a compound according to Claim-1, its derivatives, its analogs, its tautomeric forms, its stereoisomers, its geometric forms, its N-oxides, its polymorphs, its pharmaceutically acceptable salts, or solvates.

4. A pharmaceutical composition according to Claim-3, in the form of a tablet, capsule, powder, lozenges, suppositories, syrup, solution, suspension or injectable, administered in, as a single dose or multiple dose units.

5. Use of compound of general formula (I), as defined in Claim-1 or a pharmaceutical composition as defined in Claim-3 for preparing medicaments.

6. Use of compound of general formula (I), as defined in Claim-1 or a pharmaceutical composition as defined in Claim-3 for the treatment where a modulation of 5-HT melatonin activity is desired.

7. Use of a compound as claimed in Claim-1 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective action on 5-HT receptors is indicated.

8. Use of a compound as claimed in Claim-1 for the treatment and/or prevention of clinical conditions such as anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse, panic attacks, reproduction, glaucoma, sleep disorders and also disorders associated with spinal trauma and /or head injury.

9. Use of a compound as claimed in Claim-1 for the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

10. Use of a compound as claimed in Claim-1 for the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis.

11. Use of a compound as claimed in Claim-1 to reduce morbidity and mortality associated with the excess weight.

12. Use of a radiolabelled compound as claimed in Claim-1, as a diagnostic tool for modulating 5-HT receptor function.

13. Use of a compound as claimed in Claims 1 in combination with a 5-HT re-uptake inhibitor, and / or a pharmaceutically acceptable salt thereof.

14. A compound of the general formula (1), its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts and its pharmaceutically acceptable solvates for preparing a medicament.

15. A method for the treatment and/or prophylaxis of clinical conditions such as anxiety, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse, panic attacks, reproduction, glaucoma, sleep disorders and also disorders associated with spinal trauma and /or head injury which comprises administering to a patient in need thereof, an effective amount of a compound of general formula (I) as claimed in Claim-1.

16. A method for the treatment and/or prophylaxis of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea which comprises administering to a patient in need thereof, an effective amount of a compound of general formula (I) as claimed in Claim-1.

17. A method for the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis using a compound of general formula (I) as claimed in Claim-1.

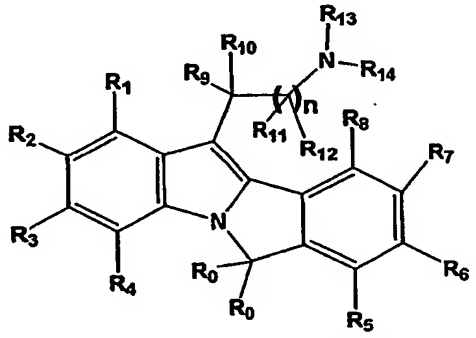
18. A method to reduce morbidity and mortality associated with the excess weight using a compound of general formula (I) as claimed in Claim-1.

19. Use of a compound as claimed in Claims 1 and/or Claim 28, in combination with either of 5-HT re-uptake inhibitor, Melatonin or Melatoninergic modulator, and / or their pharmaceutically acceptable salts so as to achieve desired therapeutic benefit.

Novel arylalkyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them.

Field of Invention:

The present invention relates to novel tetracyclic arylalkyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.



General formula (I)

The present invention also relates to the process for preparing the compounds of general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

The compounds of the general formula (I) of this invention are 5-HT (Serotonin) ligands e.g. agonists or antagonists.

Thus, compounds of general formula (I) of this invention are useful for treating diseases wherein activity of either 5-HT (Serotonin) and/or melatonin is modulated to obtain the desired effect. Specifically, the compounds of this invention are useful in the treatment and / or prophylaxis of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, depression, drug addiction, convulsive disorders, personality disorders, hypertension, autism, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders.

The compounds of general formula (I) of this invention are also useful to treat psychotic, affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs.

The compounds of general formula (I) of this invention are also useful to treat neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting. The compounds of general formula (I) of this invention are also useful in modulation of eating behavior and thus are useful in reducing the morbidity and mortality associated with excess weight.

Background of the Invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic and the serotenergic neurotransmitter systems. Serotonin has been implicated in a number of diseases and conditions, which originate in the central nervous system. These include diseases and conditions related to sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia and other bodily states. (References: Fuller, R. W., Drugs Acting on Serotonergic Neuronal Systems, Biology of Serotonergic Transmission, John Wiley & Sons Ltd. (1982), 221-247; Boullin D. J., Serotonin in Mental abnormalities (1978), 1, 316; Barchas J. et. al., Serotonin and Behavior (1973)). Serotonin also plays an important role in the peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of contractile, secretory and electrophysiologic effects.

Due to the broad distribution of serotonin within the body, there is lot of interest and use, in the drugs that affect serotonergic systems. Particularly, preferred are the compounds which have receptor specific agonism and/or antagonism for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive disorders, schizophrenia, autism, neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting (References: Gershon M. D. et. al., The peripheral actions of 5-Hydroxytryptamine (1989), 246; Saxena P. R. et. al., Journal of Cardiovascular Pharmacology (1990), supplement 7, 15).

The major classes of serotonin receptors (5-HT_{1-7}) contain fourteen to eighteen separate receptors that have been formally classified (References: Glennon et al, Neuroscience and Behavioral Reviews (1990), 14, 35 and Hoyer D. et al, Pharmacol. Rev. (1994), 46, 157-203). Recently discovered information regarding sub-type identity, distribution, structure and function suggests that it is possible to identify novel, sub-type specific agents having improved therapeutic profiles with lesser side effects. The 5-HT_6 receptor was identified in 1993 (References: Monsma et al, Mol. Pharmacol. (1993), 43, 320-

327 and Ruat M. et al, Biochem. Biophys. Res. Com. (1993), 193, 269-276). Several antidepressants and atypical antipsychotics bind to the 5-HT_6 receptor with high affinity and this binding may be a factor in their profile of activities (References: Roth et al, J. Pharm. Exp. Therapeut. (1994), 268, 1403-1410; Sleight et al, Exp. Opin. Ther. Patents (1998), 8, 1217-1224; Bourson et al, Brit. J. Pharmacol. (1998), 125, 1562-1566; Boess et al, Mol. Pharmacol., 1998, 54, 577-583; Sleight et al, Brit. J. Pharmacol. (1998), 124, 556-562). In addition, 5-HT_6 receptor has been linked to generalized stress and anxiety states (Reference: Yoshioka et al, Life Sciences (1998), 17/18, 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT_6 receptor will be useful in treating various disorders of the central nervous system.

U. S. patent 4,839,377 and U. S. patent 4,855,314 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent 2,035,310 refers to 3-aminoalkyl-1H-indole-5-thioamides and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Publication 303,506 refers to 3-polyhydropyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT_1 receptor agonists and vasoconstrictor activity and to be useful in treating migraine. European Patent Publication 354,777 refers to N-piperidinylindolylethyl-alkane sulfonamide derivatives. The compounds are said to be 5-HT_1 receptor agonists and have vasoconstrictor activity and are useful in treating cephalic pain.

European Patent Publication 438,230, refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have "5-HT_1-like" receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

European Patent Publication 313,397 refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

International Patent Publication WO 91/18897, refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

European Patent Publication 457,701 refers to aryloxy amine derivatives as having high affinity for 5-HT_{1D} serotonin receptors. These compounds are said to be useful for treating diseases related to serotonin receptor dysfunction, for example, migraine.

European Patent Publication 497,512 A2, refers to a class of imidazole, triazole and tetrazole derivatives which are selective agonists for "5-HT_1-like" receptors. These compounds are said to be useful for treating migraine and associated disorders.

International Patent Publication WO 93/00086, describes a series of tetrahydrocarbazole derivatives, as 5-HT_1 receptor agonists, useful for the treatment of migraine and related conditions.

International Patent Publication WO 93/23396, refers to fused imidazole and triazole derivatives as 5-HT_1 receptor agonists, for the treatment of migraine and other disorders.

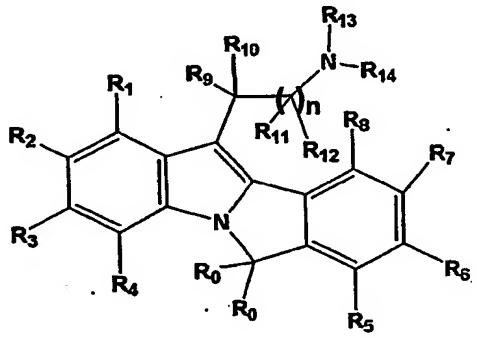
Schoeffter P. et al. refer to methyl 4-{4-[4-(1,1,3-trioxo-2H-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1H-indole-3-carboxylate as a selective antagonist for the 5-HT_{1A} receptor in their paper "SDZ216-525, a selective and potent 5-HT_{1A} receptor antagonist" European Journal of Pharmacology, 244, 251-257 (1993).

International Patent Publication WO 94/06769, refers to 2-substituted-4-piperazine-benzothiophene derivatives that are serotonin 5-HT_{1A} and 5-HT_{1D} receptor agents useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

Summary of the Invention:

The present invention relates to novel tetracyclic arylalkyl, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

More particularly, the present invention relates to novel tetracyclic arylalkyl of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them and use of these compounds in medicine.



General formula (I)

wherein R_0 is either hydrogen or linear or branched (C_1-C_2)alkyl;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, perhaloalkyl, amino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_3-C_7)cycloalkyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaralkyl, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkylthio, dialkylaminocarbonylamino,

carboxylic acid and its derivatives,

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

"n" is an integer ranging from 1 to 6. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

Partial list of such compounds of general formula (I) is as follows:

11-(2-N,N-Dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole hydrochloride salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole maleic acid salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole D,L-malic acid salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole oxalate salt;
2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt;
2-Fluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt;
2-Fluoro-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Chloro-11-(2-N-cyclopropyl-N-methylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt;
2-Fluoro-11-(2-N-cyclopropyl-N-methylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylaminoethyl)-2-methyl-6*H*-isoindolo[2,1-a]indole;
11-(2-N,N-Dimethylaminoethyl)-2-methoxy-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
2-Bromo-11-(2-N-methyl-N-cyclopropylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
4-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
3,4-Dichloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole;
1-Chloro-11-(2-N,N-dimethylaminoethyl)-4-methyl-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-(2-N,N-dimethylaminoethyl)-4-methyl-6*H*-isoindolo[2,1-a]indole;
3-Chloro-11-[(2-N-methylamino)ethyl]-4-methyl-6*H*-isoindolo[2,1-a]indole;

The compounds of general formula (I) of this invention are useful in the treatment and/ or prophylaxis of a condition wherein modulation of 5-HT and melatonin activities gives desired effect.

The present invention provides for use of the compounds of general formula (I) according to above, for the manufacture of the medicaments for the potential use in the treatment and/ or prophylaxis of certain CNS disorders such as, anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders e.g. Alzheimer's disease and age-related cognitive decline, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, panic attacks, reproduction, glaucoma, sleep disorders (including disturbances of Circadian rhythm) and also disorders associated with spinal trauma and / or head injury such as hydrocephalus. Compounds of the invention are further expected to be of use in the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The compounds of the invention are also expected to be of use in the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis.

The compounds of the invention are also expected to be of use in the modulation of eating behavior and these compounds can also be used to reduce morbidity and mortality associated with the excess weight.

The present invention provides a method for the treatment of a human or a animal subject suffering from certain CNS disorders such as, anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders e.g. Alzheimer's disease and age-related cognitive decline, ADHD (Attention Deficient Hyperactivity Disorder), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, panic attacks, reproduction, glaucoma, sleep disorders (including disturbances of Circadian rhythm) and also disorders associated with spinal trauma and /or head injury such as hydrocephalus. Compounds of the invention are

further expected to be of use in the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The present invention also provides a method for modulating 5-HT and/ or melatonin receptor function desired in certain cases.

The present invention also includes a isotopically-labelled compounds, which are identical to those defined in the general formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number found usually in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, chlorine, iodine, bromine and mTecnitium, exemplified by ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{18}F, ^{99m}Tc, ^{31}P, S, ^{123}I and ^{125}I. Compounds of present invention and pharmaceutically acceptable salts and prodrugs of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention.

Isotopically labelled compounds of the present invention are useful in drug and/or substrate tissue distribution and target occupancy assays. For example, isotopically labelled compounds are particularly useful in SPECT (single photon emission computed tomography) and in PET (positron emission tomography).

An effective amount of a compound of general formula (I) or its salt is used for producing medicaments of the present invention, along with conventional pharmaceutical auxiliaries, carriers and additives.

The present invention also relates to a pharmaceutical composition for treating and/or prophylaxis of disorders, a condition wherein modulation of 5-HT is desired in a mammal, comprising:

a. a pharmaceutically acceptable carrier
b. a compound of general formula (I) as defined above, and
c. a 5-HT re-uptake inhibitor, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

The present invention also relates to a method of treatment and/or prophylaxis of disorders, a condition wherein modulation of 5-HT is desired in a mammal, comprising:

a. a pharmaceutically acceptable carrier
b. a compound of general formula (I) as defined above, and
c. a 5-HT re-uptake inhibitor, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

The present invention also relates to a pharmaceutical composition for treating and/or prophylaxis of disorders, a condition wherein modulation of 5-HT and/or melatonin is desired in a mammal, comprising:

a. a pharmaceutically acceptable carrier
b. a compound of general formula (I) as defined above, and
c. a serotonergic or melatonergic ligand, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a serotonergic ligand), is such that the combination is effective in treating such a condition.

The present invention also relates to a method of treatment and/or prophylaxis of disorders, a condition wherein modulation of 5-HT and/or melatonin is desired in a mammal, comprising:

a. a pharmaceutically acceptable carrier
b. a compound of general formula (I) as defined above, and
c. either of a serotonergic or melatonergic ligand, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a serotonergic or melatonergic ligand), is such that the combination is effective in treating such a condition.

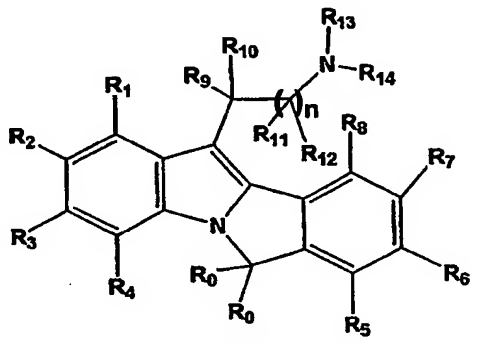
The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutical compositions containing them.

Detailed description of the invention:

The present invention relates to novel tetracyclic arylalkyl, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

More particularly, the present invention relates to novel tetracyclic arylalkyl of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their

pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them and use of these compounds in medicine.



General formula (I)

wherein R_0 is either hydrogen or linear or branched (C_1-C_2)alkyl;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, , perhaloalkyl, amino, unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_3-C_7)cycloalkyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaralkyl, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkylthio, thioalkyl, aminocarbonylamino, dialkylaminocarbonylamino, carboxylic acid and its derivatives.

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_4)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

"n" is an integer ranging from 1 to 6. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

Suitable groups represented by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be a halogen atom such as fluorine, chlorine, bromine or iodine; perhaloalkyl particularly perhalo(C_1-C_6)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, fluoroethyl, difluoroethyl and the like; substituted or unsubstituted (C_1-C_{12})alkyl group, linear or branched (C_1-C_8)alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, iso-hexyl, heptyl, octyl and the like; cyclo(C_3-C_7)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; (C_1-C_{12})alkoxy, especially, (C_1-C_6)alkoxy group such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, which may be substituted; cyclo(C_3-C_7) alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl,

furyl, pyrrolyl, oxazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1-C_6)alkyl, such as pyrrolidinylalkyl, piperidinylalkyl, morpholinylalkyl, thiomorpholinylalkyl, oxazolinylalkyl and the like, the heterocyclo(C_1-C_6)alkyl group may be substituted; heteroaralkyl group such as furanylmethyl, pyridinylmethyl, oxazolylmethyl, oxazolylethyl and the like, the heteroaralkyl

group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be substituted; acyl groups such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acyloxy group such as CH_3COO, CH_3CH_2COO, C_6H_5COO and the like which may optionally be substituted, acylamino group such as CH_3CONH, CH_3CH_2CONH, C_3H_7CONH, C_6H_5CONH which may be substituted, (C_1-C_6)monoalkylamino group such as CH_3NH, C_2H_5NH, C_3H_7NH, $C_6H_{13}NH$ and the like, which may be substituted, (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $CH_3(C_2H_5)N$ and the like, which may be substituted; arylamino group such as C_6H_5NH, $CH_3(C_6H_5)N$, $C_6H_4(CH_3)NH$, $NH\text{-}C_6H_4\text{-}Hal$ and the like, which may be substituted; arylalkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; hydroxy(C_1-C_6)alkyl which may be substituted, amino(C_1-C_6)alkyl which may be substituted; mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl group which may be substituted, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aminocarbonylamino group; (C_1-C_6)alkylaminocarbonylamino group, di(C_1-C_6)alkylaminocarbonylamino group; carboxylic acid or its derivatives such as amides, like $CONH_2$, alkylaminocarbonyl like CH_3NHCO, $(CH_3)_2NCO$, C_2H_5NHCO, $(C_2H_5)_2NCO$, arylaminocarbonyl like PhNHCO, NapthylNHCO and the like, aralkylaminocarbonyl such as $PhCH_2NHCO$, $PhCH_2CH_2NHCO$ and the like, heteroarylaminocarbonyl and heteroaralkylamino carbonyl groups where the heteroaryl groups are as defined earlier, heterocyclylaminocarbonyl where the heterocyclyl group is as defined earlier, carboxylic acid derivatives such as esters, wherein the ester moieties are alkoxycarbonyl groups such as unsubstituted or substituted phenoxycarbonyl, naphthyloxycarbonyl and the like; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group is as defined earlier, heterocycloxycarbonyl where heterocycle is as defined earlier and these carboxylic acid

derivatives may be substituted;

R_{13} and R_{14} represents hydrogen, substituted or unsubstituted linear or branched (C_1-C_{12})alkyl such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo(C_3-C_7)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; Suitable hetero cyclic rings formed between R_{13} and R_{14} along with "Nitrogen atom" be such as pyrrolyl, pyrrolidinyl, piperidinyl, pyridinyl, 1,2,3,4-Tetrahydro-pyridinyl, imidazolyl, pyrimidinyl, pyrazinyl, piperazinyl, diazolinyl and the like; the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, imidazolyl, tetrazolyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1-C_6)alkyl, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl and the like, the heterocyclo(C_1-C_6)alkyl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be further substituted.

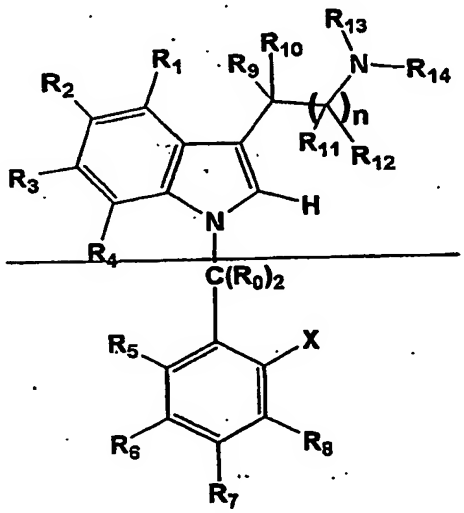
In the case of the compounds of general formula (I) having an asymmetric carbon atom the present invention relates to the D-form, the L-form and D,L-mixtures and in the case of a number of asymmetric carbon atoms, the diastereomeric forms and the invention

The above reaction is preferably carried out at a temperature of 50 °C to 150 °C. The formaldehyde can be in the form of as aqueous solution i.e. 40 % formalin solution, or a polymeric form of formaldehyde such as paraformaldehyde or trioxymethylene. When such polymeric forms are used, a molar excess of mineral acid, for example hydrochloric acid, is added to regenerate the free aldehyde from the polymer. The reaction is preferably carried in an organic solvent inert to the conditions of the reaction, such as methanol, ethanol or 3-methylbutanol and the like or a mixture thereof, and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

Scheme - 4 :

Compounds of general formula (I), may be prepared from another compound of formula (I) containing -C(=O) group/s in the side chain, by known methods of reduction to the corresponding –C(OH,H) or –C(H,H) compound; and thereafter if desired or necessary carrying out steps (i), (ii) and/or (iii) as described above.

~~Novel intermediates of general formula (II), their stereoisomers and their salts, represented as given below,~~

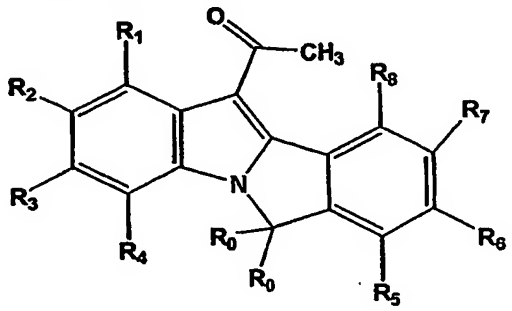


~~(II)~~

~~wherein X is halogen such chloro, bromo or iodo. R_0 is either hydrogen or linear or branched (C_1-C_2)alkyl.~~

~~R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy,~~

Novel intermediates of general formula (IV) are represented as given below,

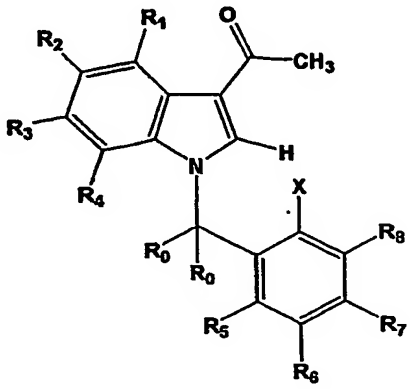


(IV)

wherein R_0,

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and 'n' are as defined previously.

The present invention also provides method to prepare intermediate of general formula (IV), which comprises of cyclizing compounds of formula (VIII),



(VIII)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as defined above; using a Pd(0) or Pd (II) derivative as a catalyst, for example tetrakis triphenylphosphine palladium, (Bis-tri-o-tolylphosphine) palladium and the like in a suitable solvent.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, Ed J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. For example, suitable protecting groups for the piperazine group include BOC, $COCCl_3$, $COCF_3$. The protecting groups may be removed according to the standard procedures.

The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The compounds of the present invention may contain one or more asymmetric centers and therefore they also exist as stereoisomers. The stereoisomers of the compounds of the present invention may be prepared by one or more ways presented below:

i) One or more of the reagents may be used in their optically active form.

ii) Optically pure catalyst or chiral ligands along with metal catalyst may be employed in the reduction process. The metal catalyst may be Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines (Principles of Asymmetric synthesis, J. E. Baldwin Ed., Tetrahedron series, 14, 311-316).

iii) The mixture of stereoisomers may be resolved by conventional methods such as forming a diastereomeric salts with chiral acids or chiral amines, or chiral amino alcohols, chiral amino acids. The resulting mixture of diastereomers may then be separated by methods such as fractional crystallization, chromatography and the like, which is followed by an additional step of isolating the optically active product by hydrolyzing the derivative (Jacques et. al., "Enantiomers, Racemates and Resolution", Wiley Interscience, 1981).

iv) The mixture of stereoisomers may be resolved by conventional methods such as microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases.

Chiral acids that can be employed may be tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, amino acids and the like. Chiral bases that can be employed may be cinchona alkaloids, brucine or a basic amino acid such as lysine, arginine and the like.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as Lithium, ammonia, substituted ammonia, sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium t-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, t-butanol, dioxane, isopropanol, isopropyl ether or mixtures thereof may be used. Organic bases such lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, salicyclic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, malic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid

and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, DMF or a lower alkyl ketone such as acetone, or the mixtures thereof.

Different polymorphs may be prepared by crystallization of compounds of general formula (I) under different conditions such as different solvents or solvent mixtures in varying proportions for recrystallization, various ways of crystallization such as slow cooling, fast cooling or a very fast cooling or a gradual cooling during crystallization. Different polymorphs may also be obtained by heating the compound, melting the compound and solidification by gradual or fast cooling, heating or melting under vacuum or under inert atmosphere and cooling under either vacuum or inert atmosphere. The various polymorphs may be identified by either one or more of the following techniques such as differential scanning calorimeter, powder X-ray diffraction, IR spectroscopy, solid probe NMR spectroscopy and thermal microscopy.

Another aspect of the present invention comprises of a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their geometric forms, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers, auxiliaries and the like.

The pharmaceutical compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parental (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or a form suitable for administration by inhalation or insufflation.

The dose of the active compounds can vary depending on factors such as the route of administration, age and weight of patient, nature and severity of the disease to be treated and similar factors. Therefore, any reference herein to a pharmacologically effective amount of the compounds of general formula (I) refers to the aforementioned factors.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional

means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of an aerosol spray from a pressurized container or a nebulizer, or from a capsule using a inhaler or insufflator. In the case of a pressurized aerosol, a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas and the dosage unit may be determined by providing a valve to deliver a metered amount. The medicament for pressurized container or nebulizer may contain a solution or suspension of the active compound while for a capsule it preferably should be in the form of powder. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of this invention, for either oral, parenteral, nasal or buccal administration, to an average adult human, for the treatment of the conditions referred to above, is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μg to 1000 μg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The affinities of the compound of this invention for the various serotonin receptors are evaluated using standard radioligand binding assays and are described here.

Radioligand binding assays for various 5-ht receptor sub-types :

i) Assay for $5HT_{1A}$

Materials and Methods:

Receptor source : Human recombinant expressed in HEK-293 cells

Radioligand : [3H]-8-OH-DPAT (221 Ci/mmol)

Final ligand concentration - [0.5 nM]

Reference compound : 8-OH-DPAT

Positive control : 8-OH-DPAT

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgSO_4$, 0.5 mM EDTA and 0.1% Ascorbic acid at room temperature for 1 hour. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_{1A}$ binding site.

Literature Reference:

- Hoyer D., Engel G., et al. Molecular Pharmacology of $5HT_1$ and $5\text{-}HT_2$ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [^{3}H]-5HT, [^{3}H]-8-OH-DPAT, [^{125}I]-Iodocyanopindolol, [^{3}H]-Mesulergine and [^{3}H]-Ketanserin. Eur. Jrnl. Pharmacol. 118: 13-23 (1985) with modifications.
- Schoeffter P. and Hoyer D. How Selective is GR 43175? Interactions with Functional $5\text{-}HT_{1A}$, $5HT_{1B}$, $5\text{-}HT_{1C}$, and $5\text{-}HT_{1D}$ Receptors. Naunyn-Schmiedeberg's Arch. Pharmac. 340: 135-138 (1989) with modifications.

ii) Assay for $5HT_{1B}$

Materials and Methods:

Receptor source : Rat striatal membranes

Radioligand : [^{125}I]Iodocyanopindolol (2200 Ci/mmol)

Final ligand concentration - [0.15 nM]

Non-specific determinant : Serotonin - [10 μM]

Reference compound : Serotonin

Positive control : Serotonin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 60 µM (-) isoproterenol at 37^0C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_{1B}$ binding site.

Literature Reference:

- Hoyer D., Engel G., et al. Molecular Pharmacology of $5HT_1$ and $5\text{-}HT_2$ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [^{3}H]-5HT, [^{3}H]-8-OH-DPAT, [^{125}I]-Iodocyanopindolol, [^{3}H]-Mesulergine and [^{3}H]-Ketanserin. *Eur. Jrnl. Pharmacol.* 118: 13-23 (1985) with modifications.
- Schoeffter P. and Hoyer D. How selective is GR 43175? Interactions with Functional $5\text{-}HT_{1A}$, $5HT_{1B}$, $5\text{-}HT_{1C}$, and $5\text{-}HT_1$ Receptors. *Naunyn-Schmiedeberg's Arch. Pharmac.* 340: 135-138 (1989) with modifications.

iii) Assay for $5HT_{1D}$

Materials and Methods:

Receptor source : Human cortex

Radioligand : [^{3}H] 5-Carboxamidotryptamine (20-70 Ci/mmol)

Final ligand concentration - [2.0 nM]

Non-specific determinant : 5-Carboxamidotryptamine (5-CT) - [1.0, µM]

Reference compound : 5-Carboxamidotryptamine (5-CT)

Positive control : 5-Carboxamidotryptamine (5-CT)

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM $CaCl_2$, 100 nM 8-OH-DPAT, 100 nM Mesulergine, 10 uM Pargyline and 0.1% ascorbic acid at 25 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the cloned $5HT_{1D}$ binding site.

Literature Reference:

- Waeber C., Schoeffter, Palacios J.M. and Hoyer D. Molecular Pharmacology of the $5\text{-}HT_{1D}$ Recognition Sites: Radioligand Binding Studies in Human, Pig, and Calf Brain Membranes. Naunyn-Schmiedeberg's Arch. Pharmacol. 337: 595-601 (1988) with modifications.

iv) Assay for $5HT_{2A}$

Materials and Methods:

Receptor source : Human Cortex

Radioligand : [^{3}H] Ketanserin (60-90 Ci/mmol)

Final ligand concentration - [2.0 nM]

Non-specific determinant : Ketanserin - [3.0 μM]

Reference compound : Ketanserin

Positive control : Ketanserin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.5) at room temperature for 90 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_{2A}$ binding site.

Literature Reference:

- Leysen J. E., Niemegeers C. J., Van Nueten J. M. and Laduron P. M. [^{3}H]Ketanserin: A Selective Tritiated Ligand for Serotonin$_2$ Receptor Binding Sites. Mol. Pharmacol. 21: 301-314 (1982) with modifications.
- Martin, G. R. and Humphrey, P. P. A. Classification Review: Receptors for 5-HT: Current Perspectives on Classification and Nomenclature. Neuropharmacol. 33(3/4): 261-273 (1994).

v) Assay for $5HT_{2C}$

Materials and Methods:

Receptor source : Pig choroid plexus membranes

Radioligand : [^{3}H] Mesulergine (50-60 Ci/mmol)

Final ligand concentration - [1.0 nM]

Non-specific determinant : Serotonin - [100 μM]

Reference compound : Mianserin

Positive control : Mianserin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM $CaCl_2$ and 0.1% ascorbic acid at 37 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to

control values in order to ascertain any interactions of test compound with the $5HT_{2C}$ binding site.

Literature Reference:

- A. Pazos, D. Hoyer, and J. Palacios. The Binding of Serotonergic Ligands to the Porcine Choroid Plexus: Characterization of a New Type of Serotonin Recognition Site. Eur. Jrnl. Pharmacol. 106: 539-546 (1985) with modifications.
- Hoyer, D., Engel, G., et al. Molecular Pharmacology of $5HT_1$ and $5\text{-}HT_2$ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [3H]-5HT, [3H]-8-OH-DPAT, [^{125}I]-Iodocyanopindolol, [3H]-Mesulergine and [3H]-Ketanserin. Eur. Jrnl. Pharmacol. 118: 13-23 (1985) with modifications.

vi) Assay for $5HT_3$

Materials and Methods:

Receptor source : N1E-115 cells
Radioligand : [^{3}H]-GR 65630 (30-70 Ci/mmol)
Final ligand concentration - [0.35 nM]
Non-specific determinant : MDL-72222 - [1.0 μM]
Reference compound : MDL-72222
Positive control : MDL-72222

Incubation conditions :

Reactions are carried out in 20 mM HEPES (pH 7.4) containing 150 mM NaCl at 25 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_3$ binding site.

Literature Reference:

- Lummis S. C. R., Kilpatrick G. J. Characterization of $5HT_3$ Receptors in Intact N1E-115 Neuroblastoma Cells. Eur. Jrnl. Pharmacol. 189: 223-227 (1990) with modifications.
- Hoyer D. and Neijt H. C. Identification of Serotonin $5\text{-}HT_3$ Recognition Sites in Membranes of N1E-115 Neuroblastoma Cells by Radioligand Binding. Mol. Pharmacol. 33: 303 (1988).
- Tyers M. B. $5\text{-}HT_3$ Receptors and the Therapeutic Potential of $5HT_3$ Receptor Antagonists. Therapie. 46:431-435 (1991).

vii) **Assay for $5HT_4$**

Materials and Methods:

Receptor source : Guinea pig striatal membranes

Radioligand : [^{3}H] GR-113808 (30-70 Ci/mmol)

Final ligand concentration - [0.2 nM]

Non-specific determinant : Serotonin (5-HT) - [30 μM]

Reference compound : Serotonin (5-HT)

Positive control : Serotonin (5-HT)

Incubation conditions :

Reactions are carried out in 50 mM HEPES (pH 7.4) at 370C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_4$ binding site.

Literature Reference:

- Grossman Kilpatrick, C., et al. Development of a Radioligand Binding Assay for $5HT_4$ Receptors in Guinea Pig and Rat Brain. Brit. J Pharmco. 109: 618-624 (1993).

viii) **Assay for $5HT_{5A}$**

Materials and Methods:

Receptor source : Human recombinant expressed in HEK 293 cells

Radioligand : [^{3}H] LSD (60-87 Ci/mmol)

Final ligand concentration - [1.0 nM]

Non-specific determinant : Methiothepin mesylate - [1.0 μM]

Reference compound : Methiothepin mesylate

Positive control : Methiothepin mesylate

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgSO_4$ and 0.5 mM EDTA at 37 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the cloned $5HT_{5A}$ binding site.

Literature Reference:

- Rees S., et al. FEBS Letters, 355: 242-246 (1994) with modifications

ix) Assay for 5HT$_6$

Materials and Methods:

Receptor source : Human recombinant expressed in HEK293 cells

Radioligand : [^{3}H]LSD (60-80 Ci/mmol)

Final ligand concentration - [1.5 nM]

Non-specific determinant : Methiothepin mesylate - [0.1 µM]

Reference compound : Methiothepin mesylate

Positive control : Methiothepin mesylate

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound(s) with the cloned serotonin - 5HT$_6$ binding site.

Literature Reference:

• Monsma F. J. Jr., et al., Molecular Cloning and Expression of Novel Serotonin Receptor with High Affinity for Tricyclic Psychotropic Drugs. Mol. Pharmacol. (43): 320-327 (1993).

x) Assay for 5-HT$_7$

Materials and Methods:

Receptor source : Human recombinant expressed in CHO cells

Radioligand : [^{3}H]LSD (60-80 Ci/mmol)

Final ligand concentration - [2.5 nM]

Non-specific determinant : 5-Carboxamidotryptamine (5-CT) - [0.1 µM]

Reference compound : 5-Carboxamidotryptamine

Positive control : 5-Carboxamidotryptamine

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound(s) with the cloned serotonin - 5HT$_7$ binding site.

Literature Reference:

• Y. Shen, E. Monsma, M. Metcalf, P. Jose, M Hamblin, D. Sibley, Molecular Cloning and Expression of a 5-hydroxytryptamine7 Serotonin Receptor Subtype. J. Biol. Chem. 268: 18200-18204.

The following description illustrates the method of preparation of variously substituted compounds of general formula (I), according to the methods described herein. These are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention.

Commercial reagents were utilized without further purification. Room temperature refers to 25 - 30 °C. Melting points are uncorrected. IR spectra were taken using KBr and in solid state. Unless otherwise stated, all mass spectra were carried out using ESI conditions. 1H NMR spectra were recorded at 300 MHz on a Bruker instrument. Deuterated chloroform (99.8 % D) was used as solvent. TMS was used as internal reference standard. Chemical shift values are expressed in are reported in parts per million (δ)-values. The following abbreviations are used for the multiplicity for the NMR signals: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, tt=triplet of triplets, m=multiplet. NMR, mass were corrected for background peaks. Specific rotations were measured at room temperature using the sodium D (589 nm). Chromatography refers to column chromatography performed using 60 – 120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions.

Description 1 : N,N-Dimethyl-1-(2'-bromobenzyl)tryptamine (D1)

A suspension of sodium hydride (9.0 mmoles, 0.36 g (60 % suspension in mineral oil), washed with THF before use), in THF was stirred and cooled at 0 – 5 °C. To this cooled solution was added a solution of N,N-dimethyltryptamine (6.0 mmoles), in THF, slowly, over 15 min., maintaining the temperature below 10 °C. After completion of addtition, the mixture was warmed to 25 – 30 °C. and maintained for 60 min. The reaction mixture was then cooled to 0 – 5 °C and solution of 2'-bromobenzyl bromide in THF (6.0 mmoles, 1.5 g in 7 mL of THF) was then added to the above well stirred mixture, maintaining the reaction temperature below 10 °C (Exothermic reaction). The reaction mixture was maintained at 20 - 25 °C for further 2 - 4 hrs. After completion of reaction (TLC), the excess of THF was distilled off and the concentrate was diluted with ice-water and extracted with ethyl acetate. Combined ethyl acetate layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure, below 50 °C.

The crude residue was purified by silica gel column chromatography using 30 % methanol in ethyl acetate as a mobile phase, to obtain the intermediate, N,N-Dimethyl-1-(2'-bromobenzyl)tryptamine, which was identified by IR, NMR and mass spectral analyses.

Description 2 – 26 (D2 – D26) :

Various indole intermediates were treated with substituted 2-bromobenzyl bromide according to the procedure described in the description 1. These compounds were identified by IR, NMR and mass spectral analyses. The following list includes list of such compounds.

List – 1:

	Description	Mass ion $(M+H)^+$
D1	2-[1-(2-Bromobenzyl)indol3-yl]ethyl-N,N-dimethylamine	357
D2	2-[1-(2-Bromobenzyl)-5-bromoindol3-yl]ethyl-N,N-dimethylamine	435
D3	2-[1-(2-Bromobenzyl)-7-bromoindol3-yl]ethyl-N,N-dimethylamine	435
D4	2-[1-(2-Bromobenzyl)-5-chloroindol3-yl]ethyl-N,N-dimethylamine	391
D5	2-[1-(2-Bromobenzyl)-5-fluoroindol3-yl]ethyl-N,N-dimethylamine	375
D6	2-[1-(2-Bromobenzyl)-7-fluoroindol3-yl]ethyl-N,N-dimethylamine	375
D7	2-[1-(2-Bromobenzyl)-5-methylindol3-yl]ethyl-N,N-dimethylamine	371
D8	2-[1-(2-Bromobenzyl)-5-methoxyindol3-yl]ethyl-N,N-dimethylamine	387
D9	2-[1-(2-Bromobenzyl)-7-methoxyindol3-yl]ethyl-N,N-dimethylamine	387
D10	2-[1-(2-Bromobenzyl)-5-bromoindol3-yl]ethyl-N,N-diethylamine	463
D11	2-[1-(2-Bromobenzyl)-5-bromoindol3-yl]ethyl-N-cyclopropyl-N-methylamine	461
D12	2-[1-(2-Bromobenzyl)-7-chloroindol3-yl]ethyl-N,N-dimethylamine	391
D13	2-[1-(2-Bromobenzyl)-6,7-dichloroindol3-yl]ethyl-N,N-dimethylamine	425
D14	2-[1-(2-Bromobenzyl)-4-chloro-7-methylindol3-yl]ethyl-N,N-dimethylamine	405
D15	2-[1-(2-Bromobenzyl)-6-chloro-7-methylindol3-yl]ethyl-N,N-dimethylamine	405
D16	2-[1-(2-Bromobenzyl)-7-trifluoromethylindol3-yl]ethyl-N,N-dimethylamine	425
D17	2-[1-(2-Bromobenzyl)-5,7-difluoroindol3-yl]ethyl-N,N-dimethylamine	393
D18	1-(2-Bromobenzyl)-3-(2-pyrrolidin-1-yl-ethyl)-1H-indole	383
D19	1-(2-Bromobenzyl)-5-bromo-3-(2-(pyrrolidin-1-yl)ethyl)-1H-indole	461
D20	1-(2-Bromobenzyl)-5-bromo-3-(2-(piperidin-1-yl)ethyl)-1H-indole	475
D21	1-(2-Bromobenzyl)-(2-(4-methylpiperazin-1-yl)ethyl)-1H-indole	412
D22	1-(2-Bromobenzyl)-5-bromo-3-(3-(pyrrolidin-1-yl)-1-hydroxypropyl)-1H-indole	491
D23	1-(2-Bromobenzyl)-5-bromo-3-(3-(piperidin-1-yl)-1-hydroxypropyl)-1H-indole	505
D24	2-[1-(2-Bromobenzyl)-7-ethylindol3-yl]ethyl-N,N-dimethylamine	385
D25	2-[1-(2-Bromobenzyl)indol3-yl]-1-hydroxyethyl-N,N-dimethylamine	373
D26	1-(2-Bromobenzyl)-5-bromo-3-(2-(4-methylpiperazin-1-yl)ethyl)-1H-indole	490

5

Example - 1 : **11-(2-N,N-Dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

1-(2'-bromobenzyl)-N,N-dimethyltryptamine (0.286 mmoles, 0.102 g) was taken in a 100 mL 3 necked round bottomed flask, along with N,N-dimethyl acetamide (40 mL), potassium acetate (0.286 mmoles, 0.281 g) and dichloro bis(tri-o-tolylphosphine)palladium (0.0143 mmoles, 0.01123 g). The reaction mixture was maintained under nitrogen atmosphere and was heated to 140-160 °C with stirring for 3-4 hrs. After the completion of reaction (TLC), excess of dimethyl acetamide was distilled off under reduced pressure.

The residue obtained was purified by silica gel column chromatography using 20 % methanol in ethyl acetate as an eluent, to afford the title compound, which was identified by IR, NMR and mass spectral analyses. The final desired compound of general formula (I) can be further purified by preparation of their acid addition salts. Melting range (°C) : 94-96; IR spectra (cm^{-1}) : 2942, 2762, 1458, 1443; Mass (m/z) : 277 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.4 (6H, s), 2.60 - 2.68 (2H, m), 3.17 - 3.26 (2H, m), 5.0 (2H, s), 7.10 - 7.77 (8H, m).

Example - 2 : **2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 76-78; IR spectra (cm^{-1}) : 2938, 2778, 1469, 1445; Mass (m/z) : 311 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.37 (6H, s), 2.59 - 2.63 (2H, m), 3.12 - 3.18 (2H, m), 5.01 (2H, s), 7.07 - 7.75 (8H, m).

Example - 3 : **2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole hydrochloride salt**

Example no. 2 (236 mg) was dissolved in 30 mL ether. To this clear solution a mixture of isopropylalcohol-hydrochloric acid (10 mL) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : >250 (dec).

Example - 4 : **2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole maleic acid salt**

Example no. 2 (228 mg) was dissolved in 30 mL ether. To this clear solution a solution of maleic acid (90 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 202 - 204 (dec).

Example - 5 : **2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole D,L-malic acid salt**

Example no. 2 (190 mg) was dissolved in 30 mL ether. To this clear solution a solution of D,L- malic acid (86 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 173 - 176 (dec).

Example - 6 : **2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole oxalate salt**

Example no. 2 (198 mg) was dissolved in 30 mL ether. To this clear solution a solution of oxalic acid (86 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 222 - 224 (dec).

Example - 7 : **2-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole citrate salt**

Example no. 2 (213 mg) was dissolved in 30 mL ether. To this clear solution a solution of citric acid (133 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 150 - 152 (dec).

Example - 8 : **2-Fluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 96-100; IR spectra (cm^{-1}) : 2941, 2784, 1458, 798; Mass (m/z) : 295 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.38 (6H, s), 2.560 - 2.65 (2H, m), 3.11 - 3.19 (2H, m), 5.02 (2H, s), 6.91 - 7.77 (8H, m).

Example - 9 : **11-(2-N,N-Dimethylaminoethyl)-2-methyl-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 102-106; IR spectra (cm-1) : 2934, 2761, 1439, 765; Mass (m/z) : 291 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 2.38 (6H, s), 2.46 (3H, s), 2.56 - 2.65 (2H, m), 3.12 - 3.20 (2H, m), 4.99 (2H, s), 6.98 - 7.73 (7H, m).

Example - 10 : **11-(2-N,N-Dimethylaminoethyl)-2-methoxy-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 140-143; IR spectra (cm-1) : 2903, 2781, 1621, 1459, 769; Mass (m/z) : 307 $(M+H)^+$; ^{1}H-NMR (δ □ppm)

: 2.40 (6H, s), 2.57 - 2.66 (2H, m), 3.13 - 3.21 (2H, m), 3.88 (3H, s), 5.00 (2H, s), 6.82 - 7.73 (7H, m).

Example - 11 : **2-Bromo-11-(2-N,N-diethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm-1) : 2964, 1613, 1444, 1261, 795; Mass (m/z) : 383 $(M+H)^+$.

Example - 12 : **2-Bromo-11-(2-N-methyl-N-cyclopropylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm-1) : 2926, 1469, 1358, 1169, 793; Mass (m/z) : 381 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 0.44-0.61 (4H,m), 1.82-1.87 (1H, m), 2.48 (3H, s), 2.72 - 2.80 (2H, m), 2.95 - 3.07 (2H, m), 5.25 (2H, s), 7.06 - 7.32 (7H, m).

Example - 13 : **4-Chloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 2938, 2778, 1469, 1445; Mass (m/z) : 311 $(M+H)^+$.

Example - 14 : **3,4-Dichloro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 345 $(M+H)^+$.

Example - 15 : **1-Chloro-11-(2-N,N-dimethylaminoethyl)-4-methyl-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 325 $(M+H)^+$.

Example - 16 : **3-Chloro-11-(2-N,N-dimethylaminoethyl)-4-methyl-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 325 $(M+H)^+$.

Example - 17 : **11-(2-N,N-Dimethylaminoethyl)-4-trifluoromethyl-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 345 $(M+H)^+$.

Example - 18 : **2,4-Difluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 84 - 86; IR spectra (cm^{-1}) : 2941, 2784, 1458, 798; Mass (m/z) : 313 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 2.38 (6H, m), 2.55 - 2.63 (2H, m), 3.09 – 3.17 (2H, m), 5.22 (2H, s), 6.63 - 7.78 (6H, m).

Example - 19 : **11-(2-Pyrrolidin-1-ylethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 86 - 90; IR spectra (cm^{-1}) : 2832, 2807, 1361, 1334; Mass (m/z) : 303 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 1.79-1.85 (4H, m), 2.55 - 2.68 (6H, m), 2.75 - 2.82 (2H, m), 5.28 (2H, s), 7.10 - 7.34 (8H, m).

Example - 20 : **2-Bromo-11-(2-pyrrolidin-1-ylethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 381 $(M+H)^+$.

Example - 21 : **11-(2-(Piperidin-1-yl)ethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared.

Melting range (°C) : 102 - 104; IR spectra (cm^{-1}) : 2929, 2840, 1455, 1162; Mass (m/z) : 317 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 1.44-1.52 (2H, m), 1.60-1.66 (4H, m), 2.38 - 2.43 (2H, m), 2.64 - 2.76 (6H, m), 5.28 (2H, s), 7.08 - 7.73 (8H, m).

Example - 22 : **11-(2-(4-Methylpiperazin-1-yl)ethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 2937, 2803, 1634, 1455; Mass (m/z) : 332 $(M+H)^+$.

Example - 23 : **11-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 333 $(M+H)^+$.

Example - 24 : **2-Bromo-11-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 425 $(M+H)^+$.

Example - 25 : **11-(2-N,N-Dimethylaminoethyl)-4-ethyl-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 305 $(M+H)^+$.

Example - 26 : **11-(2-N,N-Dimethylamino-1-hydroxyethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 293 $(M+H)^+$.

Example - 27 : **11-(2-N,N-Dimethylaminoethyl)-4-methoxy-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 307 $(M+H)^+$.

Example - 28 : **2-Bromo-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 355 $(M+H)^+$.

Example - 29 : **4-Bromo-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 355 $(M+H)^+$.

Example - 30 : **4-Fluoro-11-(2-N,N-dimethylaminoethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 295 $(M+H)^+$.

Example - 31 : **2-Bromo-11-(2-(4-methylpiperazin-1-yl)ethyl)-6*H*-isoindolo[2,1-a]indole**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 410 $(M+H)^+$.